Temporal Osseointegration: Early Biomechanical Stability Through Osseodensification

Adham M. Alifarag,[1,2] **Christopher D. Lopez,**[2,3,4,5] **Rodrigo F. Neiva,**[6] **Nick Tovar,**[2] **Lukasz Witek**[2] **Paulo G. Coelho**[2,5]

[1]College of Medicine, SUNY Upstate Medical University, Syracuse, New York, [2]Department of Biomaterials and Biomimetics, New York University College of Dentistry, 433 1st Ave, Room 862, New York, New York 10010, [3]Icahn School of Medicine at Mount Sinai, New York, New York, [4]Department of Comparative Medicine, New York University School of Medicine, New York, New York, [5]Hansjörg Wyss Department of Plastic Surgery, New York University Langone Medical Center, New York, New York, [6]Department of Periodontology, University of Florida College of Dentistry, Gainesville, Florida

Received 12 November 2017; accepted 2 March 2018
Published online in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jor.23893

ABSTRACT: Osseointegration, the direct functional and structural connection between device and bone is influenced by multiple factors such as implant macrogeometry and surgical technique. This study investigated the effects of osseodensification drilling techniques on implant stability and osseointegration using trabecular metal (TM) and tapered-screw vent (TSV) implants in a low-density bone. Six skeletally mature sheep were used where six osteotomy sites were prepared in each of the ilia, ($n = 2$/technique: Regular [R] (subtractive), clockwise [CW], and counterclockwise [CCW]). One TM and one TSV implant was subsequently placed with R osteotomy sites prepared using a conventional (subtractive) drilling protocol as recommended by the implant manufacturer for low density bone. CW and CCW drilling sites were subjected to osseodensification (OD) (additive) drilling. Evaluation of insertion torque as a function of drilling technique showed implants subjected to R drilling yielded a significant lower insertion torque relative to samples implanted in OD (CW/CCW) sites ($p < 0.05$). Histomorphometric analysis shows that the osseodensification demonstrates significantly greater values for bone-to-implant contact (BIC) and bone area fraction occupancy (BAFO). Histological analysis shows the presence of bone remnants, which acted as nucleating surfaces for osteoblastic bone deposition, facilitating the bridging of bone between the surrounding native bone and implant surface, as well as within the open spaces of the trabecular network in the TM implants. Devices that were implanted via OD demonstrated atemporal biomechanical stability and osseointegration. © 2018 Orthopaedic Research Society. Published by Wiley Periodicals, Inc. J Orthop Res

Keywords: bone; biomaterials; hip; bone tissue engineering and repair; bone/bone biology

Surgical fixation of metal implants into bone is an essential component of correcting bone deformities or fractures. This type of intervention is commonly used to rehabilitate patients to baseline function and skeletal integrity.[1] Osseointegration, the direct functional and structural connection between implant and bone, is vital in implant surgery to ensure long-term implant stability.[2] Building upon Leventhal's study on the use of titanium implants for fracture fixation,[3] Albrektsson and Branemark highlighted the osseointegrative potential of titanium in implant surgery.[2,4] Although implant and surgical protocols have evolved significantly since these landmark studies, rapid and long-lasting osseointegration remains the primary goal.[5] Successful osseointegration is dependent on an established primary stability, defined as an adequate contact between bone and implant at their interface upon instrumentation.[6] For this reason, strong primary stability, within limits, is associated with greater osseointegration.[7,8]

Primary stability, osseointegration, and secondary stability, defined as the added stability created as a result of bone healing/remodeling around an implant during the healing period, are all aspects of successful biomechanical fixation.[9] Primary stability increases resistance to micromotion of the implant, which can contribute to implant failure during healing, due to the lack of a tight fit between the implant and the osteotomy wall.[10,11] Transitioning from primary stability, secondary stability is characterized by bone remodeling around the implant as healing progresses.[12] Osseointegration is achieved when newly-formed bone is in direct contact with the implant surface without any intermediate soft tissue component.[4] Recent studies have found significant correlations between secondary implant stability and peri-implant bone density as measured by CT.[13] Under certain conditions, osseointegration may not be achieved due to several factors and this failure may compromise implant-based rehabilitation.

Failure of osseointegration continues to be a clinical challenge. Eldin et al. determined that in a cohort of implant failures related to screw complications in the thoracolumbar, lumbar, or lumbosacral spine, were either due to screw fracture or screw loosening.[14] Additionally, dental implant failure rates have been reported to be as high as ~8%,[15] due to excessive micromotion at the bone-implant interface,[16] as well as the inability to achieve functional loading.[17] Other factors, which may contribute to implant fixation failure include high microcracking frequency at osteotomy sites due to strain that exceeds bone elasticity,[18] osteonecrosis caused by thermal trauma from drilling or lack of irrigation,[19] and patient bone disease, which can create settings of low-density bone that challenge implants from forming contact with an adequate volume of bone.[20]

In order to address implant failures, understanding the contributions of each variable toward bone healing, such as surgical technique or implant feature, is

Adham M. Alifarag and Christopher D. Lopez contributed equally to this project and thus are co-first authors.
Correspondence to: Lukasz Witek, (T: 212-998-9269; F: 212-995-4244; E-mail: lukasz.witek@nyu.edu)

necessary. The fit between implant and implant bed has been described as an important surgical parameter for osseointegrative potential.[21] Other examples include geometrical configuration, implant surface characteristics such as texture, composition, or degree of porosity.[18] In addition to the aforementioned geometrical configurations, recent work has indicated that drilling protocols that differ from conventional subtractive drilling methods not only improve implant initial stability but also contributes to faster osseointegration.[22–25]

Conventional drilling protocols utilize a cutting (subtractive) technique in a clockwise direction with a positive rake angle resulting in the absence of bone residue in the osteotomy, while the non-cutting (additive) drilling technique, osseodensification (OD), has been shown to compact osteotomy site walls by means of lateral displacement of bone, thus increasing primary stability.[12,26] Furthermore, the compacting of residual bone remnants, which act as nucleating surfaces for osteoblasts around the implant, function as an autograft facilitating osseointegration.[12,25,26]

Studies assessing OD have reported positive histomorphometric results using subjects with low-density bone,[12,25,26] but studies assessing this surgical instrumentation technique in a systemic fashion are limited, prompting assessment of this drilling technique in the context of other variables essential to successful implant fixation. The objective of this study was to assess two variables (macrogeometry and surgical instrumentation) in how they contribute to the osseointegration of implants. Two different experimental implants, differing in their overall macrogeometrical configuration, one with a porous architecture—trabecular metal (TM), as porous implants have shown to osseointegrate better with surrounding bone compared to implants with a smooth surface (i.e., as machined) as the degree of roughness dictates the surface energy which contributes to osteogenic protein adsorption, cell adhesion, and cell proliferation.[27,28] While the other a more conventional implant, without the porous area—twisted screw-vent (TSV), were employed to the conventional subtractive and the additive (OD) drilling technique and their biomechanical stability and osseointegration patterns investigated.

MATERIALS AND METHODS

Preclinical Laboratory In Vivo Model

Upon receiving approval from the Institutional Animal Care and Use Committee six skeletally mature sheep (each weighing 65 ± 5 kg) were acquired and allowed to acclimate for ~5 days. Two types of implants were utilized. The first as a titanium implant with a TM network, made of elemental tantalum, occupying most of the body (Fig. 1a) (Zimmer®, Parsippany, NJ). The other implant is also a titanium implant containing a tapered screw-vent (TSV) morphology at the apex (Fig. 1b) (Zimmer®, Parsippany). Implant dimensions for the two mentioned above are 3.7 mm in diameter and 10 mm in length.

Prior to surgery, anesthesia was induced with sodium pentothal (15–20 mg/kg) in Normasol solution into the jugular vein and maintained with isoflurane (1.5–3%) in O_2/N_2O (50/50). Animal monitoring included ECG, end tidal CO_2, and SpO_2 and body temperature, which was regulated by a circulating hot water blanket. Prior to surgery, the surgical sites (bilateral hip) were shaved and iodine solution was applied to prepare surgical site. A ~10 cm incision was made to gain access to the ilium, dissections of fat tissue were performed and muscular tissue was reached. Dissection of muscular plane was performed with blunt dissection and the ilium was exposed using a periosteal elevator.

Six osteotomy sites were prepared in each of the ilia, ($n = 2$/technique: Regular [R] (subtractive), clockwise [CW], and counterclockwise [CCW]). One TM and one TSV implant was subsequently placed with R osteotomy sites prepared using a 3-step regular surgical drilling technique of 2.0 mm pilot, 2.8 mm and 3.4 mm twist drills, following Zimmer Biomet's soft bone drilling protocol, using the straight intermediate drills to the recommended final diameter.[29] CW and CCW drilling sites were subjected to osseodensification (OD) (additive) drilling using the Densah Bur (Versah, Jackson, MI) 1.7 mm pilot, 2.8 mm, and 3.8 mm multi fluted tapered burs (Fig. 2). One of each implant type was inserted into one of the two CW and two CCW prepared sites. Osteotomy site and implant placement was randomly distributed throughout the ilia to avoid site bias. All drilling techniques were performed at 1100 rpm and with saline irrigation.

The insertion torque of all implants was recorded using a digital torque meter (Tonichi STC2-G, Tonishi, Japan). Lastly, the site was closed with a layered technique using Vicryl 2–0 for muscle and 2–0 nylon for skin. Cefazolin (500 mg) was administered intravenously pre-operatively and post-operatively. Post-operatively, food and water ad libitum was offered to the animals.

All sheep were euthanized by anesthesia overdose at three weeks post-surgery. Upon sacrifice, the hips were collected by sharp dissection. Prior to further processing, removal torque (N•cm) was measured for half ($n = 36$; 18 TM implants and 18 TSV implants) the implants to measure the different implant experimental groups' stability after three weeks in vivo, while the remaining implants ($n = 36$; 18 TM implants and 18 TSV implants) were referred for histological evaluation.

Histological Preparation and Histomorphometry

Implants along with surrounding bone tissue were removed en bloc for non-decalcified histological processing. The bone-implant

(a) (b)

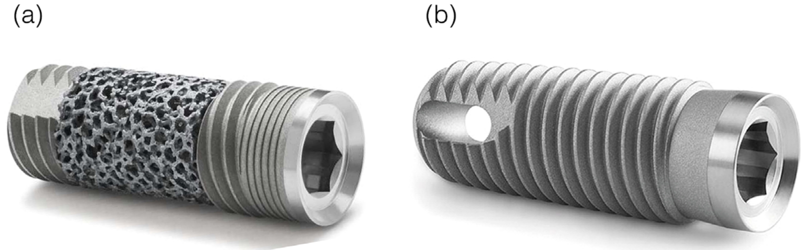

Figure 1. (a) Trabecular metal (TM) and (b) tapered-screw vent (TSV) implant morphology.

Figure 2. The CAD images of the (a) Regular (R) and (b) Versah drill, illustrating the geometric configurations.

blocks were gradually dehydrated in a series (70–100%) of ethanol solutions and then embedded in a methyl methacrylate-based resin. Embedded blocks were then cut into sections using a diamond saw (Isomet 2000, Buehler Ltd., Lake Bluff, IL). The sections were glued to slides and ground on a grinding machine (Metaserv 3000, Buehler, Lake Bluff, IL) under water irrigation with a series of SiC abrasive paper (Buehler, Lake Bluff) until they were approximately 100 μm thick. The samples were then stained in Stevenel's blue and Van Geison to differentiate the soft and connective tissues.

Samples were qualitatively and quantitatively analyzed using histology micrographs and image analysis software (ImageJ, NIH, Bethesda, MD). Bone-to-implant contact (BIC) and bone area fraction occupancy (BAFO) were quantified to evaluate the osseointegration parameters around the surface. BIC determines the degree of osseointegration by tabulating the percentage of bone contact over the entire relevant implant surface perimeter while BAFO quantifies bone growth within the implant threads as a percentage.[18,30]

Statistical Analysis

All biomechanical and histomorphometric testing data are presented as mean values with the corresponding 95% confidence interval values (mean ± CI). Insertion and removal torque, BIC value, and BAFO value data were analyzed using a linear mixed model with a fixed factor of surgical drilling method: Regular (R), clockwise (CW; OD), and counterclockwise (CCW; OD). All analyses were completed with IBM SPSS (v23, IBM Corp., Armonk, NY). By calculating the insertion torque and corresponding removal torque of the same 36 samples, a paired *t*-test comparison was used to evaluate the variation between insertion and removal torque values for half of the samples of the study.

RESULTS

No surgical site showed any sign of inflammation or infection during immediate post-operative evaluation. An exception was that the left ilium of one of the animals presented with a fracture at the study end-point, thus excluding those implants from further analyses. For the remaining intact bones, no evident failure of implants was observed at time of necropsy.

Insertion and Removal Torque

Evaluation as a function of implant type, TM implants yielded a significantly lower insertion torque (N•cm) relative to the TSV implants ($p = 0.002$) (Fig. 3a). Analysis of implant and technique showed no statistically significant differences across surgical techniques within the TM group despite higher mean values were observed for the OD (CCW and CW) techniques relative to R. The TSV implants placed in CCW osteotomies showed significantly higher value in comparison to TSV + R ($p = 0.018$) combination, and intermediate insertion torque values were observed for the TSV implants placed on the CW drilled sites (Fig. 3c).

The removal torque independent of technique, shows that TSV implants presented significantly higher removal torque values ($p = 0.008$) relative to the TM group (Fig. 4a). Removal torque measured as a function of drilling technique collapsed over implant type showed no significant differences between each drilling group (Fig. 4b). A two-level analysis of implant type and drilling technique showed that no significance was observed within each implant group ($p > 0.05$) (Fig. 4c).

When insertion (measurement at time of implant placement) and removal torque (measured after 3 weeks healing time) values were evaluated, the general trend indicated CCW and CW presented higher insertion torque values that were maintained over the 3-week period (removal torque), despite that the R drilling group osteotomy size was smaller comparing to the OD drilling group. While lower levels of insertion torque were observed for the R group implants relative to CCW and CW group implants, similar removal torque values were observed across groups irrespective of implant type. In other words, CCW and CW implants' biomechanical stability levels were kept over time at levels which R group implants only achieved after 3 weeks of bone healing and osseointegration (Fig. 3d and e).

Histomorphometric Analysis

Analysis for level of integration, with respect to BIC value results show no significant difference when data was collapsed over implant type (Fig. 5a). When evaluating for BIC as a function of drilling technique,

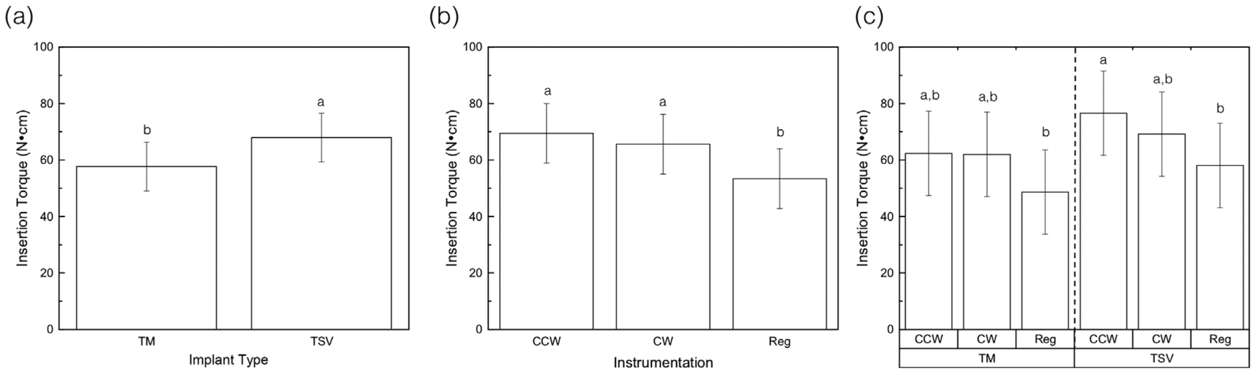

Figure 3. (a) Insertion torque measured as a function of implant type, (b) instrumentation method, (c) two-level analysis of implant type and instrumentation. The letters indicate statistically homogenous groups.

statistical differences were observed between CCW and R ($p = 0.037$), as well as CW and R group ($p = 0.005$), but no significant differences between CCW and CW groups ($p > 0.05$) (Fig. 5b). The two-factor analysis, implant type and drilling technique, presented higher mean BIC value levels for OD drilling techniques relative to R independent of implant type. Statistical analyses yielded no significant differences for the TM implants, whereas for the TSV group, there was no difference between the OD groups (CW and CCW), while the both CCW and CW showed significant differences ($p < 0.04$) when compared to the R group (Fig. 5c). Independent of implant type, samples in osteotomies prepared with OD technique (CCW and CW) consistently showed greater values for BIC relative to the control technique (Fig. 5c).

Quantitative analysis of bone within the threads, BAFO value, evaluated as a function of implant type resulted in no statistical differences between the TM and TSV implants (Fig. 5d). Evaluation of the drilling technique, shows a significant difference between both OD groups, CW and CCW, and the R group ($p = 0.001$) (Fig. 5e). The two-factor analysis of implant type and drilling technique shows that TM and TSV implants presented a significantly higher BAFO value in the OD technique when compared to the conventional R technique ($p = 0.009$ and 0.013, respectively) (Fig. 5f).

Histological Analysis

Survey histologic evaluation showed osseointegration of all implants considered for statistical analysis (Fig. 6). The mechanism of bone healing in the

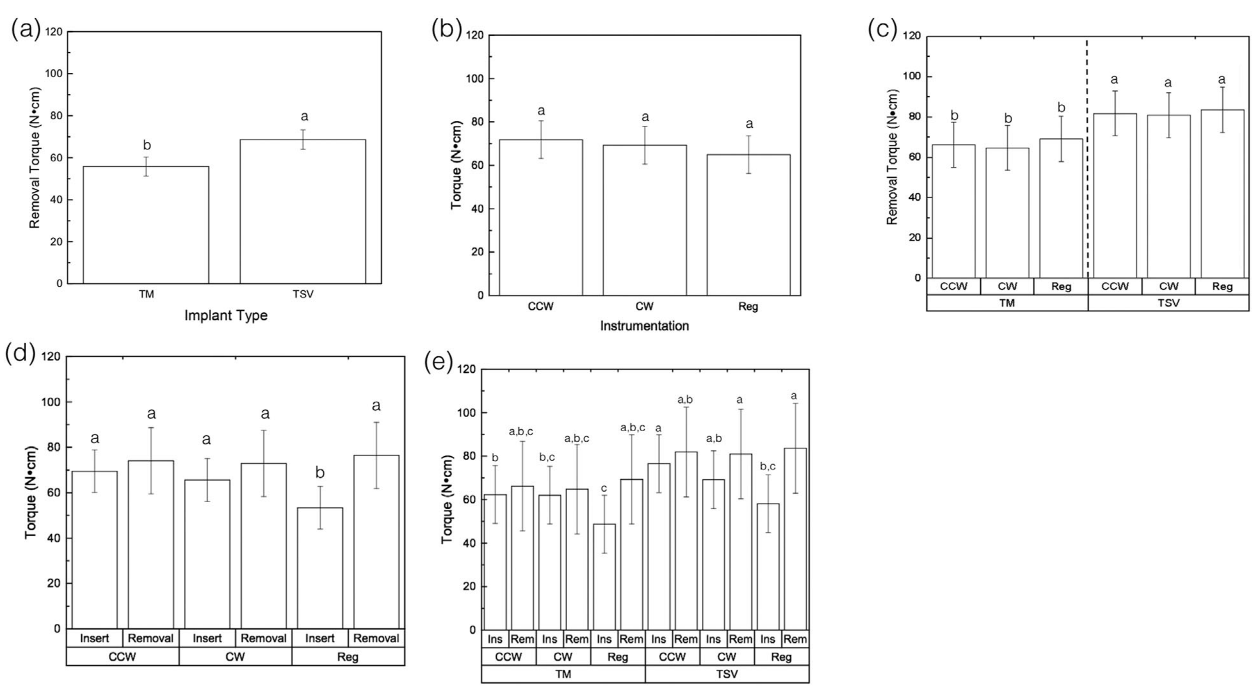

Figure 4. (a) Removal torque measured as a function of implant type, (b) overall torque values (collapsed) as a function of instrumentation, (c) two-level analysis of instrumentation and implant type, (d) insertion and removal torque measured as a function of instrumentation, (e) three-level analysis of implant type, instrumentation, and insertion/removal torque. The letters indicate statistically homogenous groups.

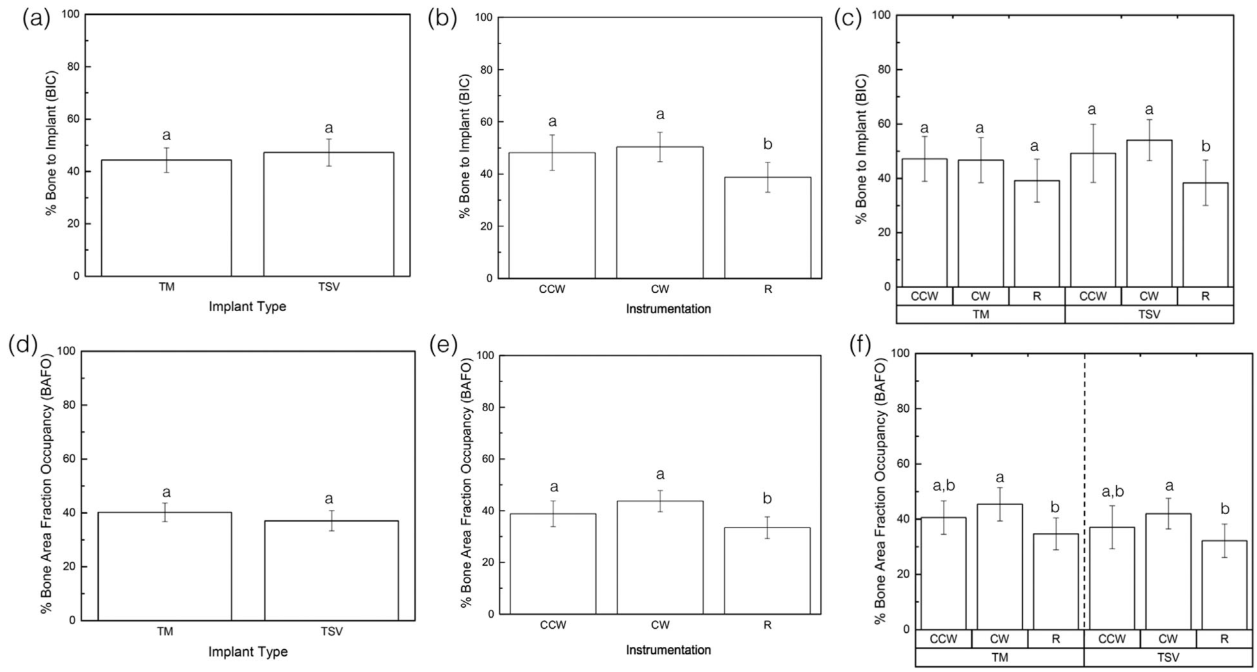

Figure 5. Histomorphometric data. BIC as a function of (a) implant type, (b) instrumentation, and (c) a compilation of implant type and instrumentation. BAFO as a function of (d) implant type, (e) instrumentation, and (f) a compilation of implant type and instrumentation. The letters indicate statistically homogenous groups.

different implant samples varied due to their respective macrogeometry. Due to the open, trabecular structure of the TM implants, while bone remnants facilitated the bridging between native bone and implant gap, bone remnants caught within the TM spaces during insertion acted as nucleating sites for osteoblastic bone deposition (Fig. 7). The TSV, due to its closed structure, followed a more conventional route in which the bone remnants facilitated the bridging of bone between the native bone and implant surface during osseointegration (Fig. 8).

All TM (Fig. 6a–c) and TSV (Fig. 6d–f) implants experimental groups presented bone in proximity with the implant surface. For the TSV implants, bone formation occurred in proximity with the threads. For the TM implants, bone formation occurred both in proximity with the implant threads as well as within the open TM spaces. Regardless of implant type, the samples drilled with the CCW and CW OD protocol presented more extensive bone tissue surrounding the implant relative to R group samples that presented a much thinner bony wall surrounding the implant. Vital bone was present within the open spaces in the TM network portion of the TM implants, suggesting successful bony ingrowth and vascularization during the healing period despite the drilling technique utilized (Fig. 7). The presence of bone remnants in the adjacent bone in the TM implant samples is most pronounced in those drilled in the CCW (Fig. 7a) orientation and least in samples drilled with the R protocol (Fig. 7c). With respect to TSV implant samples, bone remnants are seen in greater number in the CCW (Fig. 8a) and CW (Fig. 8b)-drilled samples and least in samples drilled with the regular protocol (Fig. 8c).

DISCUSSION

Osseointegration and implant stability are objectives of utmost importance because their hindrance will often lead to implant fixation failure. When complications regarding implant stability failure arise, revision surgery is often required, placing a financial burden

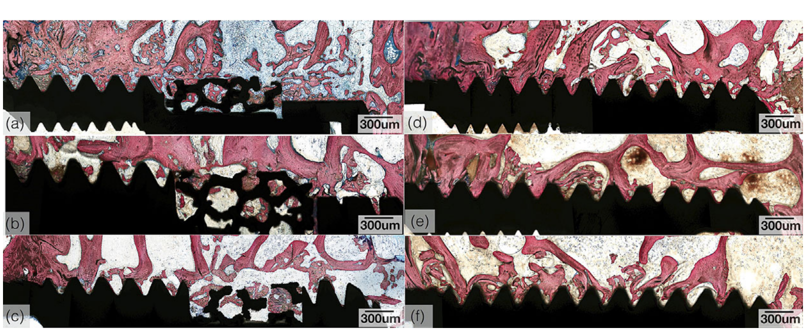

Figure 6. Survey histological micrographs for TM and TSV implants. (a) CCW-TM, (b) CW-TM, (c) R-TM, (d) CCW-TSV, (e) CW-TSV, (f) R-TSV.

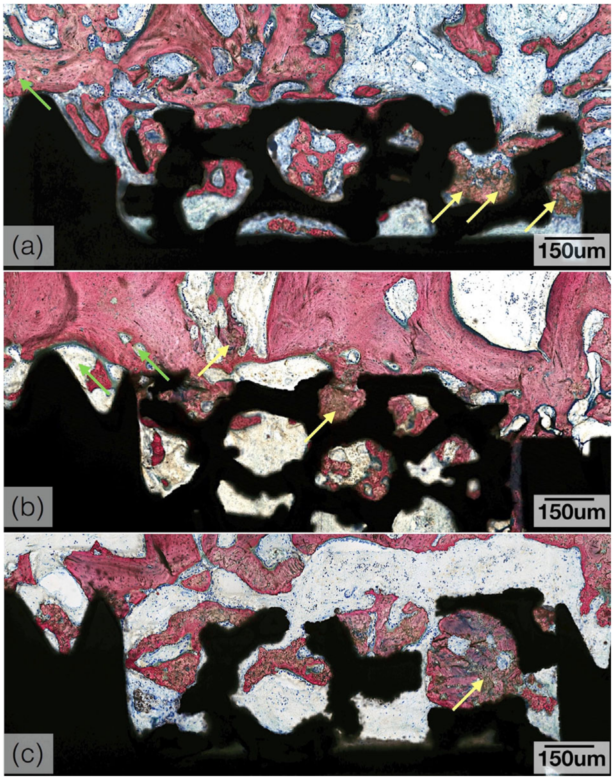

Figure 7. High magnification histological micrographs of TM implant samples. (a) CCW, (b) CW, (c) R. Yellow arrows depict bone chip residues, and green arrows depict bone remodeling sites.

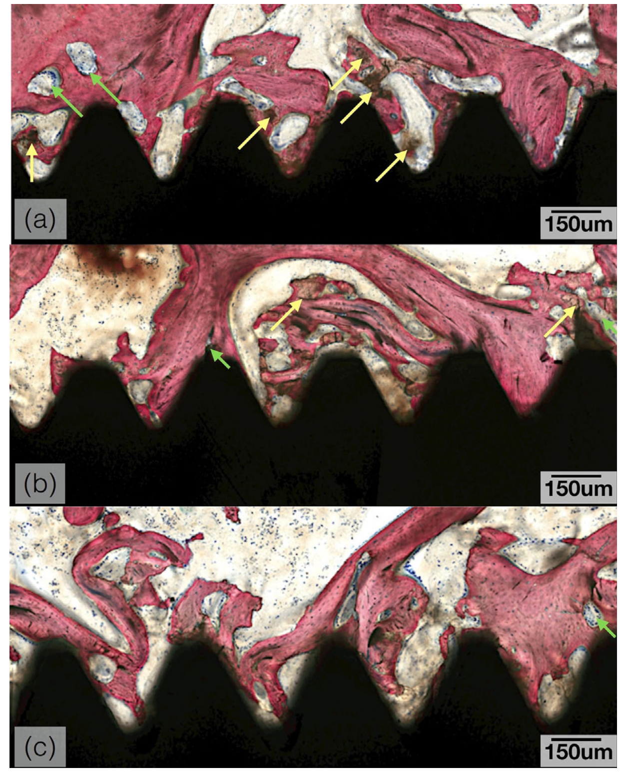

Figure 8. High magnification histological micrographs of TSV implant samples. (a) CCW, (b) CW, (c) R. Yellow arrows depict bone chip residues, and green arrows bone remodeling sites.

on the patient. For example, the mean cost for hip arthroplasty may cost nearly $15,000,[31] but a revision surgery has the potential to exceed that cost. While the cost of fixed-implant supported prosthesis has been cited at ~$1700,[32] this cost directly burdens the patient and warrants an improved treatment that will not negatively affect the patient's financial situation and quality of life.[32]

As this study was designed to take a stepwise approach of analyzing variables pertaining to instrumentation method, implant design and how they influence osseointegration and implant stability. Therefore, it was important to investigate multiple permutations of drilling direction and burrs, to investigate effects of the alternative surgical technique, (OD). As the subtractive drilling technique and burr drastically differed from the additive protocol, an intermediary protocol, utilizing a clockwise approach with the OD burr, was done to differentiate between drilling and equipment. All methods, conventional (R), CW-OD, and CCW-OD were assesed with two experimental implants, TM and TSV (Zimmer®), implants, that vastly differ in their macrogeometry.

Utilizing a highly translational large animal model for this study and selecting the hip due to its low-density bone configuration, in addition to its size,[12,33,34] allowed for the placement of all experimental groups to be nested within each subject maximizing statistical power while minimizing the number of animals. In addition, this particular region was selected because it consists of a thin cortical layer and a marrow tissue, which is comparable to human bone.[35,36] This likeness is a reason for the iliac model to be used as a site for large bone augmentation in the oral cavity.[37,38] Furthermore, the location has been previously used in studies with consistent outcomes.[35,37] Additionally, using low bone density sites makes changes in bone density over time more apparent[12,25,33] as well as it may simulate low bone density conditions such as osteoporosis.

Conventional drilling techniques limit initial bone-implant interaction due to the excavation of nucleating bone remnants, which may vary in amount due to factors such as drilling speed, time, and use of irrigation, in the osteotomy, whereas an additive drilling technique (OD) compacts the osteotomy wall without removing bone remnants.[26] These nucleating sources act as autografts on implant surfaces to promote bone regeneration.[39] Histomorphometric data suggests no significant difference between the two OD groups, but a difference is observed between OD and R group. The autografted, compacted bone observed in the OD samples lends itself to the higher torque values and quantity of bone at the bone-implant interface. These findings support the fact that OD drilling does have a significant impact, which is observed with the higher BIC and BAFO results in comparison to the conventional protocol. OD surgical instrumentation was determined to improve osseointegration and resulted in atemporal implant stability regardless of implant system evaluated stability.

Given that removal torque is comparable across all instrumentation groups (CCW, CW, and R), the lack of statistical significance suggests that OD drilling provides primary stability at day of surgery comparable to fully healed, regular drilling implants at three-weeks. Studies employing this additive drilling technique (OD) have already shown increased implant stability and bone area occupancy when compared to conventional drilling techniques; the findings of this work are consistent to this growing body of data.[1,12,26]

Differences observed between implant types were attributed to the variation in healing patterns and osseointegration due to the implant macro-architecture. Although the TM component of the TM implant has been described to present high coefficient of friction,[40] an intrinsic property of elemental tantalum present along the implant bulk, the TSV implant showed significantly greater values for both insertion and removal torque. This is likely attributed to the presence of implant threads; the TM implant has fewer threads than the TSV implant, and the presence of the resulting healing chambers has been shown to contribute to greater biomechanical fixation due to the surface area that lends itself to osseointegration. A removal torque significantly higher than the insertion torque indicates that bone healed/remodeled, integrated with the implant surface during the healing period, and thus provided stronger anchorage of the implant.[25]

Extensive new bone formation is observed in the CCW samples for both the TM and TSV implants. As implants are torqued in, they develop a strain on the surrounding bone which, if exceeds bone elasticity, can cause microcracks which contribute to bone remodeling.[18] This remodeling is vital for osseointegration to manifest, however, extreme strain causing more microcracking will yield more remodeling which facilitates failure of osseointegration by diminished bone-implant interaction. The significantly higher insertion torque observed for the OD techniques were most likely due to the compaction-autografting and the formation of the autograft bone wall comprised of compacted native bone, which has shown to create a spring-back effect and enhance implant insertion torque.[26] This explains that despite the significantly higher torque, however, the histologic sections around the OD instrumented implants did not show higher incidence of microcracking or remodeling due to compression relative to conventional drilling. The presence of autogenous bone remnants is observed in OD drilling, further supporting previous osseodensification studies that have shown that such non-vital bone remnants have been shown to be remnants of viable bone that acted as autografts to promote bone formation around the implant during the healing period.[12,39]

In clinical practice, orthopedic and dental implant complications have been reported to be as high as ~34%[14] and ~8%,[15] respectively. Of the 34% failure rate in orthopedic procedures, 16% were attributed to screw loosening during the healing period which is believed to be caused by failure to establish primary stability at the time of instrumentation, or lack of osseointegration during the healing period. Our findings suggest that these issues can potentially be minimized with the use of the osseodensification protocol as it allows for higher insertion torque, atemporal stability, and higher degrees of osseointegration.

Future studies comprising longer time points are suggested to assess changes in osseointegration over time. Further understanding of this technique and how its strengths can be maximized can potentially improve on time-sensitive clinical settings requiring osseointegration. One limitation present in this study was that no load was placed on implanted devices and therefore dynamic load-bearing implant data for the OD process is absent.

AUTHORS' CONTRIBUTIONS

AMA was one of two students helping process the samples after the in vivo experimentation. Upon finishing the processing, he and Mr. Lopez both did all the qualitative analysis, and drafted the manuscript. CDL was one of two students helping process the samples after the in vivo experimentation. Upon finishing the processing, he and Mr. Alifarag both did all the qualitative analysis, and drafted the manuscript. RN provided insight into the project, performed the procedures and helped with the qualitative analysis of results. He also helped edit the manuscript for submission. NT assisted during the surgical procedures. He also guided Mr. Alifarag and Lopez during the writing and analysis portion. Dr. Tovar also assisted in formatting and editing draft for submission. LW helped oversee the project from beginning to end. He guided the students during the processing and data gathering. Dr. Witek did the statistical analysis and data processing. He contributed to the methods, results and discussion section. Dr. Witek also organized the graphs and histological images, and formatted the manuscript for submission. PGC lead the project from conceptualization, as well as lead all of the surgical procedures, helped draft and edit the paper for submission. All aforementioned authors have read and approved the final submitted manuscript.

REFERENCES

1. Lopez CD, Alifarag AM, Torroni A, et al. 2017. Osseodensification for enhancement of spinal surgical hardware fixation. J Mech Behav Biomed Mater 69:275–281.
2. Albrektsson T, Branemark PI, Hansson HA, et al. 1981. Osseointegrated titanium implants. Requirements for ensuring a long-lasting, direct bone-to-implant anchorage in man. Acta Orthop Scand 52:155–170.
3. Leventhal GS. 1951. Titanium, a metal for surgery. J Bone Joint Surg Am 33-a:473–474.
4. Branemark PI. 1983. Osseointegration and its experimental background. J Prosthet Dent 50:399–410.
5. Parithimarkalaignan S, Padmanabhan TV. 2013. Osseointegration: an update. J Indian Prosthodontic Soc 13:2–6.

6. Campos FE, Gomes JB, Marin C, et al. 2012. Effect of drilling dimension on implant placement torque and early osseointegration stages: an experimental study in dogs. J Oral Maxillofac Surg 70:e43–e50.
7. Ottoni JM, Oliveira ZF, Mansini R, et al. 2005. Correlation between placement torque and survival of single-tooth implants. Int J Oral Maxillofac Implants 20:769–776.
8. Trisi P, Todisco M, Consolo U, et al. 2011. High versus low implant insertion torque: a histologic, histomorphometric, and biomechanical study in the sheep mandible. Int J Oral Maxillofac Implants 26:837–849.
9. Yamaguchi Y, Shiota M, Munakata M, et al. 2015. Effect of implant design on primary stability using torque-time curves in artificial bone. Int J Implant Dent 1:21.
10. O'Sullivan D, Sennerby L, Jagger D, et al. 2004. A comparison of two methods of enhancing implant primary stability. Clin Implant Dent Relat Res 6:48–57.
11. Turkyilmaz I, Aksoy U, McGlumphy EA. 2008. Two alternative surgical techniques for enhancing primary implant stability in the posterior maxilla: a clinical study including bone density, insertion torque, and resonance frequency analysis data. Clin Implant Dent Relat Res 10:231–237.
12. Lahens B, Neiva R, Tovar N, et al. 2016. Biomechanical and histologic basis of osseodensification drilling for endosteal implant placement in low density bone. An experimental study in sheep. J Mech Behav Biomed Mater 63:56–65.
13. Turkyilmaz I, Tumer C, Ozbek EN, et al. 2007. Relations between the bone density values from computerized tomography, and implant stability parameters: a clinical study of 230 regular platform implants. J Clin Periodontol 34:716–722.
14. Mohi Eldin MM, Ali AM. 2014. Lumbar transpedicular implant failure: a clinical and surgical challenge and its radiological assessment. Asian Spine J 8:281–297.
15. Siebers D, Gehrke P, Schliephake H. 2010. Delayed function of dental implants: a 1- to 7-year follow-up study of 222 implants. Int J Oral Maxillofac Implants 25:1195–1202.
16. Degidi M, Perrotti V, Piattelli A. 2006. Immediately loaded titanium implants with a porous anodized surface with at least 36 months of follow-up. Clin Implant Dent Relat Res 8:169–177.
17. Chrcanovic BR, Albrektsson T, Wennerberg A. 2014. Immediate nonfunctional versus immediate functional loading and dental implant failure rates: a systematic review and meta-analysis. J Dentistry 42:1052–1059.
18. Coelho PG, Jimbo R. 2014. Osseointegration of metallic devices: current trends based on implant hardware design. Arch Biochem Biophys 561:99–108.
19. McCann PA, Sarangi PP, Baker RP, et al. 2013. Thermal damage during humeral reaming in total shoulder resurfacing. Int J Shoulder Surg 7:100–104.
20. Linder L, Carlsson A, Marsal L, et al. 1988. Clinical aspects of osseointegration in joint replacement. A histological study of titanium implants. J Bone Joint Surg Br 70:550–555.
21. Harris WH, White RE, Jr., McCarthy JC, et al. 1983. Bony ingrowth fixation of the acetabular component in canine hip joint arthroplasty. Clin Orthop Relat Res 176:7–11.
22. Lahens B, Neiva R, Tovar N, et al. 2016. Biomechanical and histologic basis of osseodensification drilling for endosteal implant placement in low density bone. An experimental study in sheep. J Mech Behav Biomed Mater 63:56–65.
23. Lopez CD, Alifarag AM, Torroni A, et al. 2017. Osseodensification for enhancement of spinal surgical hardware fixation. J Mech Behav Biomed Mater 69:275–281.
24. Huwais S, Meyer E. 2017. Osseodensification: a novel approach in implant preparation to increase primary stability, bone mineral density and bone to implant contact. Int J Oral Maxillofac Implants 32:27–36.
25. Trisi P, Berardini M, Falco A, et al. 2016. New osseodensification implant site preparation method to increase bone density in low-density bone: in vivo evaluation in sheep. Implant Dent 25:24–31.
26. Huwais S, Meyer EG. 2017. A novel osseous densification approach in implant osteotomy preparation to increase biomechanical primary stability, bone mineral density, and bone-to-implant contact. Int J Oral Maxillofac Implants 32:27–36.
27. Martin J, Schwartz Z, Hummert T, et al. 1995. Effect of titanium surface roughness on proliferation, differentiation, and protein synthesis of human osteoblast-like cells (MG63). J Biomed Mater Res Part A 29:389–401.
28. Kieswetter K, Schwartz Z, Dean D, et al. 1996. The role of implant surface characteristics in the healing of bone. Crit Rev Oral Biol Med 7:329–345.
29. Le Gall MG. 2004. Localized sinus elevation and osteocompression with single-stage tapered dental implants. Int J Oral Maxillofacial Implants 19:431–437.
30. Leonard G, Coelho P, Polyzois I, et al. 2009. A study of the bone healing kinetics of plateau versus screw root design titanium dental implants. Clin Oral Implants Res 20:232–239.
31. Vanhegan IS, Malik AK, Jayakumar P, et al. 2012. A financial analysis of revision hip arthroplasty: the economic burden in relation to the national tariff. J Bone Joint Surg Br 94:619–623.
32. Palmqvist S, Owall B, Schou S. 2004. A prospective randomized clinical study comparing implant-supported fixed prostheses and overdentures in the edentulous mandible: prosthodontic production time and costs. Int J Prosthodontics 17:231–235.
33. Galli S, Jimbo R, Tovar N, et al. 2015. The effect of osteotomy dimension on osseointegration to resorbable media-treated implants: a study in the sheep. J Biomater Appl 29:1068–1074.
34. Jimbo R, Tovar N, Yoo DY, et al. 2014. The effect of different surgical drilling procedures on full laser-etched microgrooves surface-treated implants: an experimental study in sheep. Clin Oral Implants Res 25:1072–1077.
35. Stübinger S, Mosch I, Robotti P, et al. 2013. Histological and biomechanical analysis of porous additive manufactured implants made by direct metal laser sintering: a pilot study in sheep. J Biomed Mater Res Part B: Appl Biomater 101:1154–1163.
36. Stübinger S, Biermeier K, Bächi B, et al. 2010. Comparison of Er: yAG laser, piezoelectric, and drill osteotomy for dental implant site preparation: a biomechanical and histological analysis in sheep. Lasers Surg Med 42:652–661.
37. Jimbo R, Tovar N, Yoo DY, et al. 2014. The effect of different surgical drilling procedures on full laser-etched microgrooves surface-treated implants: an experimental study in sheep. Clin Oral Implants Res 25:1072–1077.
38. Langhoff J, Voelter K, Scharnweber D, et al. 2008. Comparison of chemically and pharmaceutically modified titanium and zirconia implant surfaces in dentistry: a study in sheep. Int J Oral Maxillofacial Surg 37:1125–1132.
39. Jimbo R, Tovar N, Marin C, et al. 2014. The impact of a modified cutting flute implant design on osseointegration. Int J Oral Maxillofac Surg 43:883–888.
40. Zhang Y, Ahn PB, Fitzpatrick DC, et al. 1999. Interfacial frictional behavior: cancellous bone, cortical bone, and a novel porous tantalum biomaterial. J Musculoskeletal Res 3:245–251.